REVIEW

Dynamic risk assessment in patients with differentiated thyroid cancer

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Abstract

The stratification of patients with differentiated thyroid cancer based on their initial risk of recurrence, according to specific clinical, histopathological and perioperative data, is an important starting point for tailoring the follow-up during the first 1–2 years after initial therapy (surgery with or without radioiodine ablation). However, risk of recurrence re-stratification based on new clinical data that becomes available after considering the response to treatment (dynamic risk assessment) provides a more accurate prediction of the status at final follow-up and a more individualized approach. In this review, we summarized the available data regarding dynamic risk of recurrence and the suggested management of differentiated thyroid cancer patients according to the response to treatment. The use of this strategy is crucial to avoid overtreatment and intensive follow-up of the vast majority of patients who will have a very good prognosis and, on the other hand, focus therapeutic efforts on those patients who will have a worse prognosis. In the future, molecular biology analysis of the tumors and well-designed prospective studies will probably refine the risk of recurrence prediction.

Key Words

- risk of recurrence
- dynamic risk
- thyroid cancer
- differentiated thyroid cancer

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Introduction

Differentiated thyroid carcinoma (DTC) is the most common endocrine neoplasia, accounting for nearly 2% of all types of cancer (Kitahara & Sosa 2016). Papillary thyroid carcinoma is the most common variant of thyroid cancer, followed by the follicular variant (Kitahara & Sosa 2016). Multiple staging systems have been developed to predict the risk of mortality in patients with DTC. The 2015 American Thyroid Association (ATA) guidelines (Haugen *et al.* 2016) recommend the AJCC/UICC TNM staging system for DTC patients based on its utility in predicting disease mortality. The estimated 10-year disease-specific survival (DSS) rate considering the recently published TNM 8th edition is 98–100% for stage I, 85–95% for stage II, 60–70% for stage III and <50% for stage IV patients (Amin *et al.* 2017, Tuttle *et al.* 2017). Assuming that the great majority of DTC patients will have a 10-year overall

survival above 95%, in the last decade, the European Thyroid Association (Pacini *et al.* 2006), the ATA (ATA Guidelines Taskforce *et al.* 2009) and the Latin American Thyroid Society (Pitoia *et al.* 2009) among other societies, adopted the risk of recurrence (RR) classification (Fig. 1). These stratification systems take into account the histopathological report, intraoperative findings, as well as preoperative and immediate postoperative relevant data. This information allows physicians to tailor the response to treatment and then, the need for a close follow-up, mainly based on the probability of having persistent/recurrent structural disease.

While this initial RR stratification settles a starting point to guide an initial follow-up course for DTC patients, it represents a static picture that does not consider the response to initial treatment after thyroid surgery with or

Modified risk of recurrence classification from
the ATA 2009 Guidelines Risk or recurrence classification from
the ATA 2009 Guidelines **Figure 1**

Risk of recurrence classifications from the 2009 and 2015 American Thyroid Association guidelines for differentiated thyroid cancer management. Left panel: Feature with the reported frequency of structural incomplete response presented in parentheses. Right panel: risk of structural incomplete response in parenthesis is presented for each category of the risk of recurrence. ATA, American Thyroid Association; *Braf*, *BRAF* oncogene; ETE, extrathyroidal extension; FTC, follicular thyroid cancer; RR, risk of recurrence; N1, lymph node metastasis; PTC, papillary thyroid cancer; *TERT*, *TERT* oncogene.

without radioiodine remnant ablation (RA) (Tuttle *et al.* 2010). This re-stratification of the initial RR based on new clinical data that becomes available during the initial follow-up is called dynamic risk assessment. As expected, this strategy would provide a more accurate prediction of the RR and a more individualized approach (Tuttle *et al.* 2010).

Using initial risk assessment in differentiated thyroid cancer

After completing initial therapy (thyroid surgery with or without RA), patients with a diagnosis of DTC are classified as having low, intermediate or high RR (Fig. 1).

The 2009 ATA RR stratification system (Fig. 1) was validated in different cohorts of DTC patients around the world (Tuttle *et al.* 2010, Castagna *et al.* 2011, Vaisman *et al.* 2012, Pitoia *et al.* 2013). These studies demonstrated

that the percentage of structural incomplete response (evidence of local or distant persistent/recurrent disease) at the end of follow-up was 3–9% for low-risk patients, 13–45% for intermediate-risk patients and 60–80% for high-risk patients. In addition, the percentage of excellent response (no evidence of clinical or biochemical disease at final follow-up) was 78–91% in low-risk patients, 52–64% in intermediate-risk patients and 31–32% in high-risk patients (Tuttle *et al.* 2010, Castagna *et al.* 2011, Vaisman *et al.* 2012, Pitoia *et al.* 2013, Haugen *et al.* 2016).

In 2016, this 2009 ATA risk stratification system was updated (Fig. 1) in the modified risk stratification system from the 2009 ATA guidelines, which considered a series of additional clinical-pathological situations: number of vascular invasion foci, number and size of the lymph nodes involved, presence of extranodal extension and *BRAF/TERT* mutational status, when available (Haugen *et al.* 2016). The Modified Stratification System from ATA 2009 guidelines was also validated in several cohorts of

patients around the world (Pitoia *et al.* 2015, Momesso *et al.* 2016, Abelleira *et al.* 2017, Park *et al.* 2017). In an investigation performed in 63 patients with low and intermediate RR from our hospital, we concluded that additional histopathological variables proposed by this new stratification system allowed for a greater refinement in the prediction of the different responses to treatment (Pitoia *et al.* 2018).

As another important feature, some authors consider the measurement of serum thyroglobulin (Tg) at 6 weeks postoperatively as a data belonging to the initial RR assessment (Tarasova & Tuttle 2016). Although a cut-off point for this value has not been clearly established yet, a non-stimulated (under thyroid hormone therapy) Tg level greater than 5 ng/mL would alert about the possibility of local or distant metastasis and could, for example, in low- and intermediate-risk patients, guide the decision for RA (Tarasova & Tuttle 2016).

A few studies have explored the age at diagnosis as a variable related to the RR in DTC patients. Our group analyzed the impact of age at the diagnosis of DTC on the frequency of structural incomplete response, considering the Modified Stratification System from ATA 2009 guidelines (Pitoia *et al.* 2017). In this study, we did not find any age threshold that could distinguish an older group of patients with a higher risk for structural incomplete response neither at the initial response to treatment nor at the end of follow-up. However, a tendency toward a lower frequency of structural incomplete response was observed at the end of follow-up in patients with intermediate and high RR less than 40 years, without statistical significance. Indeed, other authors demonstrated that age was a key predictor for the response to therapy in patients with high RR (Shah *et al.* 2018). Moreover, high-risk younger patients with a structural incomplete response to therapy had a significantly better disease specific survival (DSS) than older patients (74 vs 12%, respectively, $P < 0.001$) (Shah *et al.* 2018).

The RR classification system was also validated in patients with low and intermediate risk or recurrence who did not receive RA. With a median follow-up of 5–10 years, the percentage of structural disease in patients receiving total thyroidectomy without RA was less than 1–2% in low-risk patients and 8% in those with intermediate RR (Vaisman *et al.* 2011a, Durante *et al.* 2012, Schwartz *et al.* 2012, Momesso *et al.* 2016, Abelleira *et al.* 2017, Park *et al.* 2017, 2018, Cho *et al.* 2018), similarly to what it was reported in patients who received total thyroidectomy and RA.

This initial RR is an important starting point for the management of a patient during the first 1–2 years after initial therapy. However, additional data in the follow-up (Tg and anti-Tg values or structural disease detected by imaging) can change this static RR. For example, in a patient initially classified as having an intermediate RR who achieves an excellent response (absence of biochemical and structural disease) within 2 years after initial therapy, the current likelihood of having persistent disease will be lower than that expected with the initial static RR classification. This example shows that the real RR of a patient with DTC is a dynamic process that is modified according to the responses to therapy that the patient obtains during follow-up and that the absence of complete data to establish the initial RR could be overcome when we have the response to therapy (La Greca *et al.* 2017).

Dynamic risk assessment in differentiated thyroid cancer

Patients treated with total thyroidectomy and radioiodine RA

The dynamic RR approach implies the re-stratification of the initial RR of DTC patients considering the different responses to treatment: excellent, indeterminate, biochemical incomplete and structural incomplete (Table 1), using specific data obtained during follow-up: Tg and anti-Tg values, results of imaging studies, including neck ultrasound (US), RAI scans, computed tomography (CT) or 18-fluorodeoxyglucose positron emission tomography-CT (18-FDG PET/CT), and so forth, guided by initial RR assessment (Fig. 1).

Considering the initial response to treatment, a patient who achieves an excellent response will have a very low risk of having structural disease (1–4%) in the long-term follow-up (Tuttle *et al.* 2010, Castagna *et al.* 2011, Durante *et al.* 2012, Hong *et al.* 2014, Pitoia *et al.* 2015, Haugen *et al.* 2016, Kowalska *et al.* 2016, Trimboli *et al.* 2017, Jeon *et al.* 2018, Lee *et al.* 2018, Schlumberger *et al.* 2018, Dehbi *et al.* 2019). On the contrary, 50–85% of patients with an initial structural incomplete response, and probably independently of the initial RR, will have persistent disease, despite additional treatments (Tuttle *et al.* 2010, Castagna *et al.* 2011, Hong *et al.* 2014, Pitoia *et al.* 2015, Haugen *et al.* 2016, Kowalska *et al.* 2016, Trimboli *et al.* 2017, Lee *et al.* 2018, Schlumberger *et al.* 2018, Dehbi *et al.* 2019).

Table 1 Response-to-therapy definitions according to the initial treatment performed in patients with differentiated thyroid cancer.

	Total thyroidectomy + RA	Total thyroidectomy without RA^a	Lobectomy^a
Excellent	Non-stimulated Tg level <0.2 ng/mL Stimulated Tg level <1 ng/mL Undetectable anti-Tg Negative imaging	Non-stimulated Tg level <0.2 ng/mL Undetectable anti-Tg Negative imaging	Stable non-stimulated Tg level <30 ng/mL Undetectable anti-Tg Negative imaging
Indeterminate	Non-stimulated Tg level 0.2–1 ng/mL Stimulated Tg level 1–10 ng/mL Stable or declining TgAb levels Nonspecific findings on imaging studies	Non-stimulated Tg level 0.2–5 ng/mL Stable or declining TgAb levels Nonspecific findings on imaging studies	Stable or declining TgAb levels Nonspecific findings on imaging studies
Biochemical incomplete	Non-stimulated Tg level >1 ng/mL Stimulated Tg level >10 ng/mL Increasing anti-Tg levels Negative imaging	Non-stimulated Tg level >5 ng/mL Increasing anti-Tg levels Negative imaging	Non-stimulated Tg level >30 ng/mL Increasing Tg or anti-Tg levels Negative imaging
Structural incomplete	Structural or functional evidence of disease		

^aTSH stimulation is not recommended in patients without radioiodine remnant ablation.
RA, radioiodine remnant ablation.

The dynamic risk approach was initially proposed by Michael Tuttle from the Memorial Hospital of New York (Tuttle *et al.* 2010). This was a retrospective study of 588 patients with DTC who received total thyroidectomy and RA, with a median follow-up of 7 years (range 1–15 years). They were initially stratified by the RR of the ATA 2009 guidelines (ATA Guidelines Taskforce *et al.* 2009). After this initial RR assessment, the best response to treatment obtained during the first 2 years after initial therapy was analyzed. After the re-stratification, among patients who had an initial excellent response, the probability of having structural incomplete response was reduced from 3 to 2% in low-risk patients, from 18 to 2% in intermediate-risk patients, and, which was more remarkable, from 66 to 14% in patients with high RR (Tuttle *et al.* 2010). On the contrary, having an initial structural or biochemical incomplete response increased the percentage of persistent structural disease at the end of follow-up to 13% in low-risk patients, 41% in intermediate-risk patients and 79% in high-risk patients (Tuttle *et al.* 2010). Moreover, the authors compared the static stratification considering the initial RR and the dynamic risk assessment using the proportion of the variance explained (PVE), which measures the ability of a classification system to predict the final response (structural incomplete vs excellent response). As expected, the PVE was 34% when the initial RR was considered and it increased to 84% when the

responses to treatment during the first 2 years after initial therapy were analyzed.

These data were then validated in another retrospective cohort of 512 patients. In this study, the percentage of patients who achieved complete remission at the end of follow-up was 90% for those with low risk and 96% for those with low dynamic risk (patients who had an initial excellent response to therapy) (Castagna *et al.* 2011), and, a more important finding was that the percentage of complete remission in patients with intermediate-high-risk dropped from 60 to 27% in those with high dynamic risk (patients with initial biochemical persistence or structural incomplete response). The positive predictive value (PPV) was 72% for the dynamic risk stratification compared to 39% for the initial RR stratification, which means that the dynamic risk assessment had a better ability to predict the recurrence/persistence of disease. Accordingly, the recurrence rate after complete remission was low (2.7%), and there were no statistically significant differences between the initial low and high RR patients. This good prognosis in patients with an excellent initial response to treatment regardless of the initial RR was replicated in other studies (Hong *et al.* 2014, Pitoia *et al.* 2015, Kowalska *et al.* 2016, Jeon *et al.* 2018) (Table 2).

The dynamic risk stratification system also proved to be associated with the progression-free survival (PFS). In a retrospective cohort of 398 patients with DTC,

Table 2 Summary of studies analyzing dynamic risk assessment in patients with differentiated thyroid cancer treated with total thyroidectomy and radioiodine remnant ablation.

	No. of patients	Patients included	Median follow-up (months)	Persistent/recurrent disease based on each response-to-therapy category
Tuttle et al. 2010	588	All-risk patients	84	Exc 4% IR 0% BIR/SIR 57%
Castagna et al. 2011	512	All-risk patients	81.6	Exc 3.4% BIR/SIR 66%
Hong et al. 2014	398	All-risk patients	128	Exc 1.3% SIR 75.9%
Pitoia et al. 2015	149	Low- and intermediate-risk patients	72	Exc 1.6% BIR/SIR 31.8%
Kowalska et al. 2016	916	All-risk patients	84	Exc 1.2% IR/BIR/SIR 16.2%
Trimboli et al. 2017	201	Low- and intermediate-risk patients	29	onT4-Tg <0.28 ng/mL ^a : 0% onT4-Tg >0.28 ng/mL ^a : 52% Exc 0.5% IR 37.5% BIR 50% SIR 85.7%
Jeon et al. 2018	1359	Patients with excellent response	104.4	Exc 1%
Lee et al. 2018	667	PTC 1–4 cm	124	Exc 4.1 IR 17.6% BIR 53.4% SIR 81.5%
Schlumberger et al. 2018^b	726	Low-risk patients	64.8	Exc 0.16% All initial responses 0.5%
Dehbi et al. 2019^b	434	T1–T3 N0/N1/Nx M0 (TNM 6th ed.)	78.4	Exc 0%; all initial responses 4.8%
van Velsen et al. 2019	236	High-risk patients	72	Exc 14%
Tian et al. 2019	767	High-risk patients	67.2	Pre-ablation s-Tg <1 ng/mL and negative anti-Tg: 2.9%

^aThyroglobulin on levothyroxine treatment measured at 6–12 months after radioactive iodine; ^bProspective trials.

BIR, initial biochemical incomplete response; Exc, initial excellent response; IR, initial indeterminate response; PTC, papillary thyroid carcinoma; SIR, initial structural incomplete response; s-Tg, stimulated thyroglobulin; Tg, thyroglobulin.

through a multivariate analysis, it was found that the factors involved in the dynamic risk (stimulated Tg values >1 ng/mL and TSH suppressed Tg values >1 ng/mL) but not those involved in static RR (extranodal extension, presence of lymphadenopathy and histological type), were associated with PFS ([Hong et al. 2014](#)). More recently, a retrospective study of 762 patients with PTC measuring 1–4 cm revealed that dynamic risk assessment using data obtained from the first 2 years after initial treatment was an independent risk factor for structural recurrence during the follow-up period and that the disease-free survival (DFS) curves of each response-to-therapy category of the dynamic risk stratification system showed significant differences ($P < 0.001$) ([Lee et al. 2018](#)).

These results demonstrate the superiority of the dynamic risk in the prediction of the final response to treatment over the static initial RR. Evidence from observational and prospective studies validating the dynamic risk stratification system in patients with total thyroidectomy and RA is presented in [Table 2](#).

Management implications of the response-to-therapy categories

As it happened with the initial RR, the response to treatment can be used to guide the management of patients with DTC ([Fig. 2](#)).

An excellent response is generally achieved in 86–91% of patients with low RR, 57–63% of those with intermediate RR and in 14–16% of those with high RR who received RA ([Tuttle et al. 2010](#), [Castagna et al. 2011](#), [Vaisman et al. 2012](#), [Pitoia et al. 2013](#), [Haugen et al. 2016](#), [Kowalska et al. 2016](#), [Lee et al. 2018](#), [Schlumberger et al. 2018](#), [Dehbi et al. 2019](#), [van Velsen et al. 2019](#)). When a low-risk patient has an excellent response to treatment, although it is reassuring, the therapeutic implication in the dynamic risk assessment does not change substantially, since the risk of structural incomplete response was initially low in this group of patients. From 631 patients who had a complete ablation in the ESTIMABL1 study, only one patient had a structural incomplete response during follow-up (0.16%) ([Schlumberger et al. 2018](#)). This is a very strong data coming from a prospective study, consistent with the previously published retrospective experience in patients who received RA.

In patients with intermediate RR, on the other hand, an excellent response implies a substantial reduction of the probability of a structural incomplete response compared to that expected from their initial RR: from 36–43% to 1–2% ([Tuttle et al. 2010](#), [Castagna et al. 2011](#), [Vaisman et al. 2012](#), [Pitoia et al. 2013](#), [2015](#)). Another study ([Trimboli et al. 2017](#)) showed that the optimized threshold of baseline Tg (on T4-Tg) measured 6–12 months after initial treatment in patients with low

Figure 2

Risk of structural disease at the end of follow-up and management recommendations for each response-to-therapy category. *For some authors, the percentage of structural incomplete response at final follow-up might be higher in patients with an initial high risk of recurrence and a more strict follow-up should be recommended in this group of patients (Tuttle *et al.* 2010, Shah *et al.* 2018). CT, computed tomography; 18-FDG-PET/CT, positron emission tomography with 18-FDG integrated with computed tomography; MKI, multikinase inhibitor therapy; US, ultrasound.

and intermediate RR was set by ROC curves analysis at 0.28 ng/mL. Having onT4-Tg <0.28 ng/mL at 6–12 months after treatment was associated with longer disease free survival and absence of relapse during follow-up (odds ratio 0.328, $P=0.0001$). Another study of 226 patients with low- and intermediate-risk PTC who had an excellent response found ultrasonographically suspicious neck lymph nodes in only 1.2% of patients at 3 years and in 1.8% at the last visit. Additionally, 75% of the nodal lesions were likely false positive and none required treatment (Grani *et al.* 2019). These data support the idea that low- and intermediate-risk PTC patients with an excellent response can be safely followed with clinical assessments and unstimulated serum Tg determinations with no need of routine neck ultrasonography assessment.

On the other side, in the few high-risk patients who achieve an excellent response, several authors have demonstrated that the percentage of structural incomplete response at the end of the follow-up would also be low (1–3%) (Castagna *et al.* 2011, Jeon *et al.* 2018). According to these investigations, an excellent response would be maintained at the end of follow-up, independently of the

initial RR. On the contrary, other authors showed that an excellent response to treatment in patients with initial high RR supposes a RR of 5–15% (Tuttle *et al.* 2010, Shah *et al.* 2018, van Velsen *et al.* 2019). Therefore, a closer follow-up and additional structural or functional imaging would be necessary to rule out disease that may not be detected by US and Tg measurements prior to classify these patients as having an excellent response (Haugen *et al.* 2016, Tarasova & Tuttle 2016). Additionally, in a cohort of 67 ATA high-risk patients who achieved an immediate excellent response (pre-ablation stimulated Tg <1 ng/mL), which occurred in 9% of cases, the structural incomplete response was only 3% after a median follow-up of 5.6 years (regional lymph node metastases in all cases) (Tian *et al.* 2019). The suggested management for patients with an excellent response to treatment can be seen in Fig. 2.

The persistence of Tg levels >1 ng/mL under levothyroxine therapy, stimulated Tg levels >10 ng/mL or rising anti-Tg in the absence of structural disease (biochemical incomplete response) in patients who received RA occurs in 11–19% of low RR patients, 21–22% of those with intermediate RR and in 16–18% of those with

high RR (Tuttle *et al.* 2010, Castagna *et al.* 2011, Vaisman *et al.* 2012, Pitoia *et al.* 2013). In general, these patients have a good prognosis, given that the majority (56–68%) will achieve an excellent response at final follow-up, 19–27% will continue with detectable Tg or anti-Tg values and only 8–17% will develop structural disease during 5–10 years of follow-up (Tuttle *et al.* 2010, Castagna *et al.* 2011, Vaisman *et al.* 2011b, 2012, Pitoia *et al.* 2013, 2014). The management in this group of patients can also be observed in Fig. 2, but in general will depend on the trend of the Tg/anti-Tg levels over time. Rising Tg or anti-Tg levels should prompt the use for additional imaging methods (tomography, 18-FDG-PET/CT, for example). On the contrary, declining Tg or anti-Tg values would require only routine observation and neck US every 2–3 years. The TSH goal should be 0.5–1 mIU/L (Haugen *et al.* 2016).

The presence of a structural incomplete response is observed in only 2–6% of patients with low RR, in 19–28% of those with intermediate RR and in the majority (67–75%) of those with high RR (Tuttle *et al.* 2010, Castagna *et al.* 2011, Vaisman *et al.* 2012, Pitoia *et al.* 2013, Kowalska *et al.* 2016, Lee *et al.* 2018, Schlumberger *et al.* 2018, Dehbi *et al.* 2019). The majority of these patients (around two-thirds) will remain in this category despite additional therapy/ies (surgery, radioiodine). The site of the persistent disease, the rate of progression, the radioiodine avidity and the response to previous therapy will condition the patient's management: surgery, external beam radiation therapy, tyrosine kinase inhibitors or, in selected cases, active surveillance. The target TSH value in this group is <0.1 mIU/L, except in cases of atrial fibrillation, where values between 0.1 and 0.5 mIU/L are acceptable (Fig. 2) (Haugen *et al.* 2016).

An indeterminate response to therapy (Table 1) occurs in 12–29% of patients with low RR, 8–23% in the intermediate RR group and only in 0–4% of those with high RR (Tuttle *et al.* 2010, Vaisman *et al.* 2012). A retrospective study of 128 PTC patients which investigated the presence of risk factors for indeterminate response showed that patients with a rhTSH-stimulated Tg greater than 2 ng/mL prior to radioiodine ablation were almost four times more likely to have an indeterminate response than those with a rhTSH-stimulated Tg ≤2 ng/mL (Jeong *et al.* 2019). The management usually consists of observing nonspecific findings or small elevations of the Tg or anti-Tg level until the patient can eventually be reclassified in any of the above categories, maintaining a TSH level in the 0.5–1 mIU/L range. Similar to what happens with the biochemical

incomplete response, only 13–20% of cases will develop structural disease in 10 years of follow-up (Fig. 2) (Haugen *et al.* 2016). A recent study found that out of 145 DTC patients with indeterminate response-to-therapy followed up for a median time of 68 months, 9% had biochemical or structural incomplete response. In this subgroup of patients, unstimulated Tg values steadily increased (mean percentage change +27.1% at each follow-up visit) independently from the baseline levels (Malandrino *et al.* 2019). These data denote that in patients with indeterminate response, the trend of unstimulated Tg values may be useful to identify patients who will present with a higher risk for persistent disease.

Patients treated with total thyroidectomy or lobectomy without radioiodine RA

In the 2015 ATA guidelines, lobectomy is proposed as the initial surgical approach for tumors <1 cm without extrathyroidal extension and clinically N0, and may be sufficient for low-risk papillary and follicular carcinomas up to 4 cm in the absence of aggressive features (Haugen *et al.* 2016). Moreover, considering that RA is not routinely recommended in low RR patients and that it should be considered in those with intermediate RR, a significant percentage of patients with DTC will not receive RA after initial surgery.

The first validation of the dynamic risk assessment in patients with DTC without RA was performed in 2016 (Momesso *et al.* 2016), based on a retrospective cohort of 507 patients, 320 treated with total thyroidectomy and 187 with lobectomy. As expected, 85.4% of patients had low RR and 14.6% intermediate RR. The authors demonstrated that the percentage of persistence/recurrence of the disease at the end of the follow-up (median 8.4 years) was 0 in those with an excellent response, 1.3% in those who had an indeterminate response, 31.6% in patients with a biochemical incomplete response and 100% in patients with structural incomplete response. In a similar cohort of non-ablated patients ($n=357$, median follow-up 8.6 years) other group demonstrated that DFS was significantly different according to the initial response to treatment (Park *et al.* 2017). This clearly demonstrated that the dynamic risk stratification also allows to predict the risk of structural disease during follow-up in patients who did not receive RA.

It is worth to mention that although almost 18–30% of the patients who did not receive RA in the different cohorts have an initial indeterminate response, only 1.3–1.6% will have a final structural incomplete response

(Momesso *et al.* 2016, Abelleira *et al.* 2017, Park *et al.* 2017, Cho *et al.* 2018, Lee *et al.* 2018). This is different from what happens in patients who receive RA, where the percentage of structural disease in patients with indeterminate response reaches 20% (Tuttle *et al.* 2010, Vaisman *et al.* 2012). This would suggest that nonspecific ultrasonographic findings, slightly elevated Tg values or stable/declining anti-Tg levels in patients who did not receive RA would have very little impact on the persistence/recurrence rate.

An initial biochemical response (Table 1) was associated with a low probability of structural disease in patients with total thyroidectomy without RA, similar to what happens in patients who received RA (0 vs 8–17%) (Momesso *et al.* 2016, Park *et al.* 2017). In contrast, in patients treated with lobectomy, the presence of an initial biochemical incomplete response (non-stimulated Tg level >30 ng/mL, Table 1) was associated with a 50% frequency of structural incomplete response. However, all these patients achieved an excellent response after additional therapy (surgery with or without RA) (Momesso *et al.* 2016). Interestingly, the postoperative serum Tg levels of 208 patients with low-risk PTC who underwent lobectomy was also evaluated, and it was found that there was no significant differences in serum Tg level changes between patients with or without recurrent disease (Park *et al.* 2018). Therefore, periodic measurements of serum Tg levels would not be useful for predicting recurrent disease in these patients and decreased or stable serum Tg levels do not guarantee a lower probability of recurrence. However, only two patients of the cohort from this study had Tg measurement >30 ng/mL and both had recurrent disease, which probably means that this cut-off value would still be indicative of a high probability of persistent structural disease (Park *et al.* 2018). Similarly, a retrospective study of 619 patients with papillary thyroid cancer treated with lobectomy (median follow-up of 103 months), showed that the anti-Tg status, the Tg levels or the changing trend of Tg/anti-Tg levels were not significantly associated with structural recurrence (Cho *et al.* 2018). Moreover, in this study of patients treated with lobectomy alone, each response to therapy category was not well correlated with the incidence of structural recurrence, and the PVE of the dynamic stratification system in these patients was only 32.4%, which is similar to what it was reported for the initial RR assessment in patients who received total thyroidectomy and RA (Tuttle *et al.* 2010).

As expected, all patients with low and intermediate RR who did not receive RA and had a structural incomplete response after initial evaluation (1–2.9%) will maintain

this response at the end of follow-up (Momesso *et al.* 2016, Abelleira *et al.* 2017, Park *et al.* 2017, Cho *et al.* 2018, Lee *et al.* 2018).

On the other hand, patients without RA who have an initial excellent response have very low percentages of structural incomplete response at the end of follow-up, similar to what happens in patients who receive RA. In fact, none of the patients from the cohort of Momesso *et al.* who had an initial excellent response presented with structural evidence of disease at final follow-up, and only 2/256 (0.78%) patients of the cohort from Park *et al.* who had an initial excellent response, had recurrence of the disease 4 and 5 years after lobectomy (Momesso *et al.* 2016, Park *et al.* 2017).

There is little evidence to guide TSH targets or the use of thyroid hormone in ATA low-risk patients who have undergone lobectomy. The 2015 ATA guidelines suggest a TSH goal of 0.5–2 mU/L. However, a recent study demonstrated that postoperative serum TSH levels did not affect recurrence in low-risk PTC patients who underwent thyroid lobectomy (Lee *et al.* 2019). If we consider that 73% of patients will have TSH >2 mU/L at 1 year after lobectomy (Cox *et al.* 2018), many patients following the ATA recommendation will be unnecessarily treated with levothyroxine. Therefore, the decision for TSH suppression in this group of patients should be made in terms of patient-specific considerations (Lee *et al.* 2019). A review on the indications and follow-up of patients undergoing lobectomy for DTC was recently published (Park & Yoon 2019).

A summary of the studies analyzing dynamic risk assessment in patients treated with total thyroidectomy or lobectomy without RA can be seen in Table 3.

Dynamic risk assessment in children and adolescents

DTC is the most common endocrine tumor in children and adolescents; it represents 1% of tumors in prepubertal children, a percentage that increases to 7% in patients between 15 and 19 years old (Verburg *et al.* 2017). In the pediatric age, DTC frequently is diagnosed as an advanced disease that exceeds the limits of the thyroid gland, with loco-regional metastases to the cervical lymph nodes and very frequently, with distant metastases to the lungs. These children also have a high frequency of recurrence, especially in those under 10 years old (Verburg *et al.* 2017). Despite this fact, the 10-year survival rate is 98–99% (Demidchik *et al.* 2006).

Until now, there is no widely validated postoperative staging system in pediatric patients (Francis *et al.* 2015).

Table 3 Summary of studies analyzing dynamic risk assessment in differentiated thyroid cancer patients treated without radioiodine ablation.

	No. of patients	Patients included	Median follow-up (months)	Persistent/recurrent disease based on each response-to-therapy category
Momesso <i>et al.</i> 2016	TT: 320 L: 187	Low risk: 433 Intermediate risk: 74	100.5	Exc 0% IR 1.3% BIR 31.6% SIR 100%
Park <i>et al.</i> 2017	TT: 64 L: 293	Low risk: 187 Intermediate risk: 170	103.2	Exc 0.78 IR 1.5% BIR 16.7% SIR 100%
Abelleira <i>et al.</i> 2017	TT: 88	Low risk: 78 Intermediate risk: 10	28	Exc 0% IR 5.6%
Lee <i>et al.</i> 2018	TT: 26 L: 69	Low and intermediate risk	124	Exc 7.4% IR 0% BIR 0% SIR 100%
Cho <i>et al.</i> 2018	L: 619	Low risk: 340 Intermediate risk: 279	103	Exc 1.6% IR 3.8% BIR 2.9% SIR 100%

BIR, initial biochemical incomplete response; Exc, initial excellent response; IR, initial indeterminate response; L, lobectomy; SIR, initial structural incomplete response; TT, total thyroidectomy.

The AJCC/TNM system has little utility, given that all patients will be classified as stage I (absence of distant metastasis) or II (presence of distant metastasis) (Amin *et al.* 2017). The 2015 ATA Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer proposes to categorize children into low, intermediate and high risk in order to identify the risk of persistence of the disease and then design the strategy for postoperative follow-up (Francis *et al.* 2015). In this classification, the low-risk group includes patients with intrathyroidal tumors without lymph node metastases or patients with incidental N1a disease (microscopic metastasis to a 'small number' of central neck lymph nodes). The intermediate group is defined as having 'extensive' lymph node metastasis in the central compartment or 'minimal' number of lymph nodes in the lateral compartment. On the other hand, patients with locally invasive tumors, 'extensive' lateral lymph node involvement, or distant metastases belong to the high-risk group. This classification is unclear, given that the number of lymph nodes considered as 'minimal' or 'extensive' involvement is not specified. In a cohort of 77 DTC patients <18 years, 64 with total thyroidectomy and RA and 13 with lobectomy, the dynamic risk stratification system was assessed using the classification of RR for pediatric patients proposed by the ATA guidelines (Sung *et al.* 2017) and the responses to treatment proposed by the ATA guidelines for adult patients (Haugen *et al.* 2016). The authors considered minimal N1a disease when metastatic foci was <0.2 cm and involved in <5 lymph nodes as low risk and minimal N1b disease with <10 lymph nodes with metastatic foci <3 cm as intermediate RR. The initial excellent response ranged from 82% for low RR patients, 62% for intermediate-risk patients and 4% for high-risk patients. On the other

hand, although the risk of having structural incomplete response at the end of follow-up was significantly higher in the high-risk group (65%), this difference was not evident between low and intermediate RR patients (12 and 19%, respectively). It seems that the probability of having a structural incomplete response in low RR patients is higher in pediatric patients than in adults, who have a risk of structural disease between 2 and 6% (Sung *et al.* 2017). However, only 22% of patients in this study had a low RR. Considering the dynamic risk assessment, the excellent response at the end of follow-up was reached in 97% of the patients with an initial excellent response, in 60% of those with an initial indeterminate response, in the 40% of those who had an initial biochemical incomplete response and only 4% of those who showed an initial structural incomplete response. The majority (88%) of patients with a structural incomplete response at the end of follow-up were patients with the same response at initial evaluation. Only 1 patient (3%) with an excellent initial response had recurrence of the disease confirming the impact of the initial response, even in the pediatric population of patients with DTC (Sung *et al.* 2017).

Similar results were found by subsequent studies in pediatric patients with DTC (Sohn *et al.* 2017, Kim *et al.* 2018, Zanella *et al.* 2018, Remiker *et al.* 2019). The percentages of structural incomplete responses at the end of follow-up and excellent responses according to the initial assessments were similar to those shown in patients >18 years of age, which suggests that the dynamic risk stratification can also be used in pediatric population. It must be considered that in these cohorts, the majority (56–73%) of patients had >15 years old, a subgroup of patients that would have a more favorable prognosis in comparison with younger patients.

Future perspectives

Contributions of molecular markers to the dynamic risk assessment

In recent years, some studies have suggested the use of molecular markers to predict the RR in patients with DTC. Although not routinely recommended for initial postoperative staging, the *BRAF* mutation and others, such as *TERT* mutations, would have the potential to refine the RR estimation when interpreted in the context of other clinical-pathological risk factors (Haugen *et al.* 2016).

In a meta-analysis of 14 publications that included 2470 patients with PTC from nine different countries, the *BRAF*V600E mutation was associated with higher RR than *wild type* tumors (24.9 vs 12.6%, $P<0.00001$ (IC 95% 1.61–2.32) (Tufano *et al.* 2012). Given that this mutation is usually associated with other clinical-pathological variables such as aggressive histology, lymph node metastases and extrathyroidal extension, it is difficult to determine in which proportion the *BRAF* mutation is independently associated to an increase in the RR. On the contrary, when the mutational state of *BRAF* is associated with other clinical factors, it could be useful (Haugen *et al.* 2016). This is evident in multifocal papillary microcarcinomas with minimal extrathyroidal extension, where the presence of *BRAF* mutation increases the RR to 20% (Niemeier *et al.* 2012) (currently categorized as intermediate risk by the 2015 ATA guidelines for adult patients). In a recent study of 620 DTC patients, *BRAF* status taken together with stimulated Tg levels, measured at the time of RA, improved the performance of the ATA risk stratification system. In particular, considering the low-risk patients group, only positive *BRAF* V600E mutation combined with a stimulated Tg level measured at the time of RA >8.9 ng/mL was associated with persistent disease (Repaci *et al.* 2019).

TERT mutation, on the other hand, also turned out to be an independent predictor of DFS and mortality in patients with DTC (Melo *et al.* 2014). The inclusion of the *TERT* mutational status in the dynamic risk stratification in patients with DTC increases the prediction of structural disease (Kim *et al.* 2017b). The authors divided the cohort ($n=357$) into four groups: (1) patients with excellent response without *TERT* mutated, (2) patients with indeterminate response without *TERT* mutated, (3) patients with structural/biochemical incomplete response without *TERT* mutated or patients with excellent/indeterminate response with *TERT* mutated and

(4) patients with structural/biochemical incomplete response and *TERT* mutated. The 10-year recurrence-free survival was 94.9, 82.7, 50.2 and 23.1%, respectively ($P<0.001$), and cancer-specific survival rates were 100, 98.7, 94.2 and 76.9%, respectively. It is interesting to note that patients harboring *TERT* mutation who achieve an excellent initial response still persist with a high probability of recurrence, although the survival is not less than in the groups with non-mutated *TERT* (Kim *et al.* 2017a). This could clarify the discrepancy between some groups that report a 14% structural incomplete response in high RR patients who achieve an excellent response (Tuttle *et al.* 2010), compared to those who showed that the initial excellent response is independent of the RR (Castagna *et al.* 2011, Jeon *et al.* 2018). Following this line of thought, patients with an initial excellent/indeterminate response and *TERT* mutated (considered as harboring a high RR) should probably have a more strict follow-up. Another interesting point from this study (Kim *et al.* 2017a) is that patients with *TERT* mutated who reached a biochemical incomplete or a structural incomplete response have a very poor prognosis. The authors suggest that since this type of mutation has been associated with dedifferentiated tumors and low radioiodine avidity (Kim *et al.* 2016), patients with *TERT* mutations who do not present an excellent response might already be considered as potentially radioiodine-refractory and therefore candidates to other systemic therapies when structural disease non-amenable for surgical treatment is found (tyrosine kinase inhibitors or redifferentiation therapy) (Kim *et al.* 2016). On the other hand, the combination of *TERT* and *BRAF* mutations in the same tumor was associated with higher risk of structural incomplete response than when they were analyzed separately (Xing *et al.* 2014), suggesting that the combination of these mutations is probably more useful for improving the RR prediction.

Interestingly, a study using next-generation sequencing (NGS) found that *TERT* mutations are subclonal in the few PTCs that harbor them (9%), whereas they are clonal in poorly DTCs and anaplastic thyroid cancers (where the frequency of *TERT* mutation is 40 and 73%, respectively), denoting selection during tumor evolution (Landa *et al.* 2016). Simultaneous analysis of cancer-associated genes of interest (*BRAF*, *KRAS*, *NRAS*, *PIK3CA*, *TP53* and so forth) by using NGS could further enhance the understanding of the clinical behavior of DTC and allow a better prediction of the patient outcomes (Landa *et al.* 2016, Bandoh *et al.* 2018).

Circulating miRNAs are emerging as new blood markers of poorer prognosis in DTC. Gómez-Pérez *et al.* determined the levels of miR-146, miR-221 and miR-222 in the peripheral blood of 60 DTC patients in correlation with the dynamic risk stratification. The authors found that elevated miR-222 and miR-146 levels were associated with poorer outcomes of the disease, suggesting that these miRNA may have a prognostic value in the management and follow-up of DTC patients (Gómez-Pérez *et al.* 2019).

Existing and ongoing prospective trials

Recently, the data from the medium-term follow-up from the ESTIMABL1 trial were published (Schlumberger *et al.* 2018). This was a prospective randomized, phase 3 study in patients with low-risk thyroid cancer that compared four strategies of postoperative RA in a 2 × 2 factorial design: half of the patients were stimulated with recombinant human thyroid-stimulating hormone (rhTSH), half with 4 weeks withdrawal of thyroid hormone; within each group, half of the patients were given a low-activity (1.1 GBq; 30 mCi) or high-activity (3.7 GBq; 100 mCi) radioiodine. At 6–8 months, thyroid ablation was *complete* in 631 (92%) of 684 patients, with equivalent proportions for all four ablation strategies (Schlumberger *et al.* 2012). The outcome at 5 years showed only 2% of structural incomplete response, confirming the retrospective data already published. Additionally, this study showed that the initial disease status of each patient was strongly correlated with the stimulated thyroglobulin concentration at ablation, only 2% of patients with stimulated Tg levels lower than 5 ng/mL at the moment of RA had a structural incomplete response during follow-up (Schlumberger *et al.* 2018). These data are also consistent with the HiLo study, which showed a larger frequency of SIR (5%) after a median follow-up of 6.5 years. This is mainly attributed to the fact that there were a proportion of included patients with an intermediate RR (Dehbi *et al.* 2019). Interestingly, recurrences were still seen in HiLo study beyond 5 years suggesting that a simplified surveillance protocol with the use of serum Tg alone might be considered after 5 years of follow-up for some or even all patients (Dehbi *et al.* 2019).

These two recent prospective trials in combination with previous observational studies showed definitive evidence that low-dose RA is an acceptable therapy for DTC patients. Two large prospective trials are ongoing, the IoN trial (NCT01398085) and ESTIMABL2 (NCT01837745), including low and low-to-intermediate-risk patients

(IoN also includes patients with minimal extrathyroidal extension and N1a disease) randomly assigning to have either low-dose (30 mCi) RA or no RA, with DFS as a major endpoint. These studies will be key to clarify the need for RA in most patients with DTC.

Conclusions

The dynamic risk stratification constitutes a paradigm shift in the management of patients with DTC. In recent years, we moved from having a single treatment for all patients (total thyroidectomy, RA, regular diagnostic whole body scans, etc.) to an individualized treatment initially supported by the RR, as a result of the analysis of the first data obtained after the surgery, the histopathological study and the clinical and perioperative serum Tg/anti-Tg levels, a situation that will be modified based on the responses obtained throughout the follow-up. This approach avoids excessive treatment and intensive follow-up in the vast majority of patients who will have a very good prognosis (low risk and most of those with intermediate risk of recurrence) and, on the other hand, focus therapeutic efforts on the few patients with worse prognosis (high RR patients).

The validation of this dynamic stratification system in patients with lobectomy and patients who did not receive RA is an incentive for many endocrinologists to opt for this practice in patients with low and even for those with an intermediate RR. On the other hand, adolescents and children over 10 years of age with DTC may also be candidates for this approach, although the studies that support this approach are scarce.

In the future, more studies showing the impact of the molecular biology analysis of the surgical piece will probably further refine the RR prediction. Ongoing prospective studies will provide a more solid basis for therapeutic decisions regarding dynamic risk in this complex management of the individual patient with DTC.

Declaration of interest

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